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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,760	AUSTIN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-46 is/are pending in the application.

4a) Of the above claim(s) 18-46 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-46 are pending in the application.

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-15) in Paper No. 8 is acknowledged. The traversal is on the ground(s) that examination of additional claims would not be a burden on the Examiner. Groups I and II have been rejoined as the traversal regarding Groups I and II is persuasive. However, the search required for Groups III-V are not co-extensive with the search required for Groups I and II, which is evidence of a search burden.

The claims of Groups I and II (claims 1-17) have been rejoined and are addressed herein.

Claims 18-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Inventions.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the phrase, "a polynucleotide encoding said ER resident chaperone protein, operably linked to a promoter, is introduced into said cells" this phrase renders the claim indefinite because it is unclear if the polynucleotide or the protein is operably linked to the promoter. It is acknowledged that nucleic acids, not proteins, are operably linked to promoters. However, the language of the claim is unclear, rendering the claim indefinite.

6. Furthermore, claim 11 recites the limitation "said ER resident chaperone protein, operably linked to a promoter". As mentioned above, the claim can be interpreted to mean that said protein is operably linked to the promoter. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite ER resident chaperone protein, operably linked to a promoter.

Claims 12-15 depend upon claim 11, and are therefore rejected for the same reason.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5 and 8-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims encompass ER resident chaperone proteins which are different from those disclosed in the specific for which no written description is provided in the specification. It is note that the specification defines "ER resident chaperone protein" as "any protein , present in or associated with, the ER, that acts to facilitate the folding, assembly or translocation of proteins", the chaperones can be "naturally present in the ER or modified to be present in the ER", and also encompasses, **"any variant or derivative"** thereof (emphasis added; see page 10, line 10-23). This large genus is represented in the specification by only the named ER resident chaperone proteins. Thus, applicant has express possession of only about 8 species, in a genus which comprises hundreds of millions of different possibilities, considering every possible "variant or derivative" of every possible ER resident chaperone.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common element or attributes of the proteins are disclosed. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that:

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

> Also, in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that,

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, certain specific ER resident chaperones are described, as well as the function common to all ER resident chaperone proteins. However, the structures of all ER resident chaperones is not disclosed, nor is specific guidance on identifying the structure of any such protein.

Furthermore, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any ER resident chaperon protein other than those expressly disclosed. Therefore, the claims fail to meet the written description requirement by encompassing proteins which are not described in the specification.

9. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expressing endogenous or exogenous chaperone protein in cells *in vitro* and expressing **endogenous** chaperon protein in cells *in vivo*, does not reasonably provide enablement for expressing any **exogenous** chaperone protein in cells *in vivo* (which encompasses gene therapy). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to using a nucleic acid encoding an ER resident chaperone protein to express said protein in cell *in vivo* for therapeutic and prophylactic purposes. Therefore, the nature of the invention encompasses gene therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass a nucleic acid encoding any ER resident chaperone protein or any variant or derivative thereof.

Furthermore, the claims encompass treating any thrombin related disorder in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples including inconsistent results, the inconsistency of results in animal models and humans, vector production problems, and vector efficiency (see page 409, columns 1-2). Specifically, regarding the ideal gene therapy vector, Crystal teaches, "The vector should be specific for its target, not recognized by the immune system, stable and easy to reproduce... Finally it would express the gene (or genes) it requires for as long as required in an appropriately regulated fashion." (See p. 409, second column). Verma et al (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) reaffirms the obstacles to successful gene therapy by stating, "The hurdles to overcome in efficient gene therapy are successful gene transfer of the therapeutic genes, appropriate expression levels associated with sufficient duration of gene expression, and the specificity of gene transfer to achieve therapeutic effects in the patient." (See p. 267, under "Discussion"). Walther and Stein also indicate, "The majority of

clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

To overcome the teachings in the art, the specification would need to supply direct, correlative guidance on how to administer the gene of interest (here a gene encoding an ER resident chaperone) to a subject in such a way that the gene is specifically delivered into the appropriate cell in such a way that the gene expresses the polypeptide of interest in the cell at an appropriate level and for an appropriate duration such that administration of the gene has therapeutic of prophylactic effects in a human patient.

Working Examples and Guidance in the Specification

The specification has no working examples of therapeutic or prophylactic of a gene encoding an ER resident chaperone protein. The specification, while providing a general review of various gene delivery methods does not provide teachings sufficient to overcome doubts raised in the art with regards to methods of gene therapy. No specific teachings regarding the administration of ER resident chaperone constructs with any success is presented. No teachings are provided that the methods claimed are able to express satisfactory levels of protein over a sufficiently long term to be efficient as a therapeutic or prophylactic agent. No teachings are provided as to the dosage amount or frequency required to effectively treat any thrombin associated disorder.

Therefore, it is therefore not predictable that the claimed method would effectively achieve any therapeutic or prophylactic effect.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of the administration of a nucleic acid encoding an ER resident chaperone would require, initially, animal studies to demonstrate that the claimed method could overcome all of the obstacles to successful gene therapy recognized in the art (and mentioned above). After experimentation in the animal models, the efficacy of the treatment would have to be tested in human subjects. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the experimentation required to perform the broadly claimed method is undue.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As mentioned above, the claims are drawn to methods of expressing endogenous and exogenous protein in cells *in vitro* and *in vivo.* However, the specification only provides enablement for expressing endogenous or exogenous chaperone protein in cells *in vitro* and expressing **endogenous** chaperon protein in cells *in vivo.* The following rejections under 35 U.S.C. 102 are applied to the claims only to the extent that they encompass expressing chaperone protein in cells *in vitro,*and expressing **endogenous** chaperon protein in cells *in vivo.*

11. Claims 1, 4-8, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakai et al. (Cell Structure and Function, Vol. 20:33-39; 1995).

Nakai teaches a method comprising producing an ER resident chaperone protein in a cell (see Figure 1, p. 34; and Figure 4(b), p. 37), wherein the cell is a monocyte (here M1 cell), which differentiates into a macrophage (see p. 33, first paragraph); wherein the ER resident chaperone protein is BiP/GRP78 (see Figures 1-3, pages 34-36); wherein the ER resident chaperone protein is GRP94 (see Figures 1 and 2, pages 34-35); wherein the ER chaperone protein is produced by administering to said cell a compound that induces the expression or activation of an endogenous ER resident chaperone protein, (here the cytokine IL-6) (see Figures 1-4, pages 34-37). Although Nakai does not specifically teach that the production of the ER resident protein chaperone protein within the cell results in a decrease in the level of tissue factor procoagulant activity on the surface of the cell, it is taught that the cells express the ER resident chaperone protein; therefore, the cells would necessarily have a decrease in the level of tissue factor procoagulant activity on the cell surface.

12. Claims 1-3, 7-9 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al (Int. J. Exper. Path. Vol. 79, 1998).

Cheng teaches a method comprising producing an ER resident chaperone protein in a cell (here HSP47, see abstract; and p. 127, last paragraph); wherein the cell is an endothelial cell, (here an interstitial smooth muscle cell see abstract; and p. 128, first paragraph); wherein the ER resident chaperone protein is HSP47 (see p. see abstract; and p. 127, last paragraph); wherein the cell is present within a mammal, here a rat (see abstract and p. 126, under "animals" and "tissue collection"); wherein the ER chaperone protein is produced by administering to said cell a compound that induces the expression or activation of an endogenous ER resident chaperone protein (here gentamicin see abstract and p. 127, last paragraph);). Although Cheng does not specifically teach that the production of the ER resident protein chaperone protein within the cell results in a decrease in the level of tissue factor procoagulant activity on the surface of the cell, it is taught that the cells express the ER resident chaperone protein; therefore, the cells would necessarily have a decrease in the level of tissue factor procoagulant activity on the cell surface.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
June 3, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER